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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/805,800	03/13/2001	Joseph Sypek	WYS-006.01	2859

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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/805,800	SYPEK ET AL.	
	Examiner	Art Unit	
	Phillip Gambel	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5 and 7-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,5 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's Brief on Appeal, filed 4/15/05, is acknowledged.

However, upon an updated search, New Grounds of Rejection, including prior art under 35 USC § 102, have been set forth herein.

The examiner apologizes for any inconvenience to applicant in this matter.

2. Claims 1, 4, 5 and 7-13 are pending.

Claims 2, 3 and 6 have been canceled.

Applicant's election of the species (C) B7-1- and B7-2-specific antibodies, of the species (B) in vivo and of the species systemic lupus erythematosis in Paper No. 5, filed 7/18/02, has been acknowledged.

Claims 1, 4, 5 and 7-13 are under consideration in the instant application.

3. Claims 8-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 8-12 are indefinite in that the metes and bounds of "short", "intermediate" and "extended" course of therapy as well as "short" and "late" dosing regimens are ill-defined and unclear. These "limitations" are relative in nature and the claims do not recite and the specification does not appear to provide sufficient information on the "time frames" to apprise the ordinary artisan of the metes and bounds of the claimed methods.

Applicant is reminded that the amendment must point to a basis in the specification so as not to add any new matter. See MPEP 714.02 and 2163.06

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:
A person shall be entitled to a patent unless --

a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1, 4, 5, and 7-13 are rejected under 35 U.S.C. § 102(a)(e) as being anticipated by Chen et al. (U.S. Patent No. 5,990,109) (see entire document).

Chen et al. teach methods of treating protein tyrosine kinase-associated disorders, including lupus (e.g. see column 19, paragraph 4) comprising administering inhibitors including anti-CD80 antibody (i.e. anti-B7-1), anti-CD86 antibody (anti-B7-2) rapamycin, FK506 and cyclophosphamide (e.g. see column 21, paragraph 2; Claims, including Claims 10 and 38).

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.

Therefore, the prior art teaching of combining therapeutic agents, including anti-CD80 antibody, anti-CD86 antibody and rapamycin in the treatment of various disorders including lupus are anticipated by the prior art teaching the same agents for the same targeted diseases.

Given the various formulations and modes of administration described in Utility, particularly on columns 19-22, encompassing meeting the needs of the patients, amounts indicated in the Physician's Desk Reference as well as early, immediate and extended dosing regimens,

the claims methods of providing early, intermediate, and late dosing are anticipated by the prior art methods of treating various inflammatory diseases, including lupus, with combination therapy, including the use of anti-CD80 antibody, anti-CD86 antibody, rapamycin, FK506 and cyclophosphamide.

Although the prior art does not state "systemic lupus erythematosis" per se, the ordinary artisan would have immediately envisaged the claimed "SLE" targeted disease,

Given the prior art teachings of treating lupus by the prior art, as "SLE" was the standard or hallmark of stating "lupus" by the ordinary artisan at the time the invention was made.

There does not appear to be a manipulative difference between the methods steps of the prior art and the instant claimed methods.

7. Claims 1, 4, 5, and 7-13 are rejected under 35 U.S.C. § 102(e) as being anticipated by Co et al. (U.S. Patent No. 6,913,747) (see entire document).

Co et al. teach methods of treating various diseases, including SLE (see column 5, paragraph 3; column 22, paragraph 4) by administering anti--B7-1 antibody and (anti-B7-2 antibody), including combination with other standard therapy drugs such as rapamycin and cyclosporine (e.g. see columns 22-23, overlapping paragraph and column 24, paragraph 5).

It is noted that the claimed methods recite "comprising" which leaves the claim open for the inclusion of unspecified ingredients even in major amounts. See MPEP 2111.03.
Therefore, the prior art teaching of combining therapeutic agents, including anti-CD80 antibody, anti-CD86 antibody and rapamycin in the treatment of various disorders including lupus are anticipated by the prior art teaching the same agents for the same targeted diseases.

Given the various formulations and modes of administration described in Therapeutic Methods and Compositions on columns 21-25, encompassing administering compounds in single doses or in more than one dose over a period of time to confer the desired effect as well as the needs to meet the needs of the patients and the severity of the disease (e.g. see column 24, paragraphs 3-4),
the claims methods of providing early, intermediate, and late dosing are anticipated by the prior art methods of treating various inflammatory diseases, including lupus, with combination therapy, including the use of anti-CD80 antibody, anti-CD86 antibody, rapamycin, FK506 and cyclophosphamide.

There does not appear to be a manipulative difference between the methods steps of the prior art and the instant claimed methods.

8. Claims 1, 4, 5 and 7-13 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Co et al. (US 2002/0176855 A1) in view of de Boer et al. (U.S. Patent No. 5,747,034), Cottens et al. (WO 95/16691) (1449; #A12) and Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456) essentially for the reasons of record.

Applicant's arguments, filed in the Brief on Appeal, filed 4/15/05, have been fully considered but are not found convincing essentially for the reasons of record.

The following is reiterated for applicant's convenience.

Applicant argues that while Co et al. does generally suggest that other standard therapy drugs may also be administered with these antibodies, they provide absolutely no evidence that the co-administration of additional drugs could be advantageous. In turn, applicant asserts that this suggestion amounts to merely an unguided and speculative invitation to further experimentation, which is not the standard by which obviousness under 35 USC 103 is determined. Applicant further submits that Co et al. Does teach or suggest that rapamycin should be considered a standard therapy drug.

In addition, applicant notes that the co-administration of a B7-1 antibody with cyclosporin A successfully inhibits T cell proliferation in the absence of blocking agents for B7-2 (see column 28, lines 22-28 of DeBoer).

Therefore, applicant asserts that given that cyclosporin A can be used in combination with B7-1 antibodies as a substitute or B7-2-specific antibodies, and one would not have been motivated to use a combination of B7-1- and B7-2-specific antibodies with cyclosporin, let alone any other immunosuppressive drug.

However, it is noted that this referenced Example 14 (see columns 27-28 of DeBoer et al.) is drawn to alloantigen tolerance induction in an experimental animal model and may relate to cyclosporin sensitivity in such alloantigen signaling (see column 6, paragraph 3 of DeBoer et al..

Further, it is noted that DeBoer et al. also teach the combination of two molecules, including one that binds to B7-1 antigen and an immunosuppressive agents (see column 14, paragraphs 2-3). Here, CTLA4Ig which binds both B7-1 and B7-2, is included an agent.

As pointed out previously, Co et al. teach methods of inhibiting B7:CD28/CTLA-4 pathway, including treating autoimmune diseases such as SLE (e.g., see page 10, column 1, paragraph 4; with B7-specific antibodies, including the combination of anti-B7-1 and anti-B7-2 antibodies with other standard therapy drugs such as methotrexate, cyclosporin and steroids (page 10, columns 1-2, overlapping paragraph) (see entire documents, including Detailed Description of the Invention, particularly Therapeutic Methods and Compositions). Co et al. teach known modes of administration and pharmaceutical compositions which can be administered in a single dose or in more than one dose over a period of time to confer the desired effect, which is based on a particular patient as determined by one of ordinary skill in the art (see page 11, columns 1-2).

As pointed out previously, De Boer teach the use of anti-B7 antibodies which can be given in combination with one or more immunosuppressive agents, including immunosuppressive agents which block or inhibit the activation or proliferation of T cells, including rapamycin (see columns 14, Immunosuppressive Agents). De Boer et al. teach the use of anti-B7 antibodies to treat various diseases and conditions, including SLE (column 15, paragraph 1). Here, too, the dosage and mode of administration will depend on the individual (see column 15-16, formulation and Methods of Administration). See entire document.

Therefore, both Co et al. and DeBoer et al. Both recognize the combination of targeting both B7-1 and B7-2 in downmodulating the immune response, including in treating autoimmune diseases such as SLE at the time the invention was made.

Applicant acknowledges that DeBoer et al. suggest other immunosuppressive agents, including rapamycin, in combination with other B7-1-specific antibodies, this reference fails to teach that any other immunosuppressive agents would be effective as cyclosporin. Citing Strom et al. (Figure and Table 36.1), applicant argues that cyclosporin and rapamycin are not equivalent molecules and in turn, one of ordinary skill in the art would not be able to reasonably predict that the combination of anti-B7-1 antibodies and rapamycin would result in the increased level of survival when compared to anti-B7-1 antibodies and cyclosporin.

Applicant asserts that Cottens et al. and Strom et al. do not cure the deficiencies of Co et al. and DeBoer et al. Applicant notes that these are general references but do not suggest the claimed invention.

One cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. In re Keller , 642 F.2d 413, 208 USPQ 871 (CCPA 1981); In re Merck & Co., Inc. , 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). See MPEP 2145.

In response to applicant=s arguments that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See In re Fine 5 USPQ2d 1596 (Fed. Cir 1988) and In re Jones 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, the primary reference Co et al. and to some degree DeBoer et al. clearly provide teachings to target both B7-1 and B7-2 in immunosuppressive therapies which include other known immunosuppressives such as rapamycin, including autoimmune diseases such as SLE.

Cottens et al. teach the use of rapamycin as an immunosuppressant for various inflammatory conditions, including SLE (see entire document, including page 9, The Novel Compounds are particularly useful for the following conditions, particularly Section (b)). Cottens et al. teach the administration of rapamycin together with other immunosuppressives for treatment, including in combination with other immunosuppressive monoclonal antibodies (see page 11, paragraph 4). Consistent with the other teachings and general practice at the time the invention was made, the modes of administration and dosages will depend on the condition to be treated (e.g. the disease type or nature of resistance) for the subject in need (see page 11, paragraph 1-3) (see entire document).

In contrast to applicant's assertion, the primary and secondary references provide clear teachings of combining immunosuppressives in therapeutic regimens to inhibit the immune response including combining antibodies and rapamycin. Further, the use of immunosuppressive therapy relies upon a number of basic principles as set forth in Strom et al. (Therapeutic Immunology, Austen et al. (Ed.) Blackwell Science, Cambridge MA, 1996; see pages 451-456). These principles include that different agents are used, each of which is directed at a different molecular target and aimed at interrupting several discrete stages in the immune activation pathway, including the expectation of achieving additive-synergistic effects (e.g. see page 451 and Figure 36.1). A basic principle includes the appropriate reduction or withdrawal of an immunosuppressive drug when that drug's toxicity exceeds its therapeutic benefit (page 451, column 2, lines 1-4). Strom et al. concludes that more refined immunosuppressive regimens including targeted discrete steps in antigen recognition, signal transduction and effector immunity are anticipated in clinical application (see page 455, column 2, paragraph 2).

Therefore, the prior art provides motivation and expectation of success in combining immunosuppressives in therapeutic regimens, including the expected advantages of additive-synergistic effects and reducing toxicity of certain immunosuppressives. The strongest rationale for combining reference is a recognition, expressly or implicitly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent that some advantage or expected beneficial result would have been produced by their combination In re Sernaker 17 USPQ 1, 5-6 (Fed. Cir. 1983) see MPEP 2144

Given the clear teachings of the prior art to combine anti-B7-1 and anti-B7-2 antibodies alone or in combination with other immunosuppressive therapy to inhibit immune responses, including in therapeutic regimens of treating SLE alone in conjunction with the known use of rapamycin to treat SLE alone or in combination with other immunosuppressive antibodies, including anti-B7 antibodies; one of ordinary skill in the art at the time the invention was made would have been motivated to combine anti-B7-1 and anti-B7-2 antibodies with rapamycin to inhibit immune responses in various therapeutic regimens including the treatment of SLE at the time the invention was made. The various dosing regimens encompassed by the instant claims were obvious at the time the invention was made, given that it was well known and practice at the time the invention was made to provide immunosuppressive therapy based upon the condition and needs of the patient, as evidenced by the teachings of the prior art. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments are not found persuasive.

8. No claim allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (571) 272-0844. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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